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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/284,009	04/05/1999	CLAIRE F. LEWIS	550-128	1771

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EXAMINER
SORBELLO, ELEANOR

ART UNIT	PAPER NUMBER
1633	14

DATE MAILED: 11/28/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/284,009	LEWIS ET AL
	Examiner	Art Unit
	Eleanor Sorbello	1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language pro[illegible]

[illegible] Notice of Informal Patent Application (PTO-152)

3☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

6☐ Other: _____

U.S. Patent and Trademark Office

PTO-326 (Rev. 04-01) Office Action Summary [illegible]

DETAILED ACTION

Continued Prosecution Application

1. The request filed on September 28, 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/284,009 is acceptable and a CPA has been established. An action on the CPA follows.

Response to amendment

2. Applicant's Pre-Amendment and Supplemental amendment received on September 28, 2001 and October 17, 2001 have been filed as Paper Nos: 12 and 13. Claims 25-50 have been canceled and claims 51-86 have been added. **Claims 51-86 are currently pending and will be examined.**

Claim Objections

3. **Claims 51-86 are objected to because they contain numerous misspelled words, a few of which are stated below. A spell check is suggested, and a subsequent review of the claims for spelling errors.**

Claims 51, 55, 62, 63, 64, 69, 70-76, 78, 80-83 recite "and/or" either once or several times per claim. It is not clear which combinations are required and which are not required for the invention to work as claimed. This is also objected to as it is poor grammar.

Claims 52-74 and 76-85 are objected to because they are dependent claims and recite the term "A" instead of the term "The". It is suggested that "A" be deleted and replaced with --The--.

Claims 51 and 76, line 2 recites "clement". This is taken to be element.

Claim 55 is objected to because it recites the phrase "viral viral". This phrase is interpreted to be "viral vector".

Claim 62 recites the term "ischaeniic". This term is misspelled.

Claim 64 recites the term "mononuclclar". This term is misspelled.

Claim 69 is objected to because it recites the word "fur". This is taken to be a typographical error for the word "for". Also claim 69 recites the word "mononuclcar".

Claim 80 is objected to because it recites "regulatahlc" element. This term is taken be a typographical error for the term "regulatable".

Claim 86 recites the acronym "NOL". This is taken to be NOI.

Claim 86 also recites the term "vectori". This is taken to mean "vector".

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 69-73, 81, 82 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification

to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods for (i) selectively destroying mononuclear phagocytes; (ii) treating any condition associated with hypoxia, ischemia or stress, or any combination of hypoxia, ischemia and stress; (iii) targeting mononuclear phagocytes *in vitro* or *in vivo* ; (iv) a delivery system for targeting a mononuclear phagocyte to a target hypoxic, ischaemic or stress site, or any combination of hypoxia, ischemia and stress sites; (v) internalizing a regulatable agent into a phagocyte; and (vi) pharamceutical compositions.

The claims therefore encompass numerous hypoxic conditions wherein there is a deficiency of oxygen in the tissues. The specification prophetically states that the invention is directed at hypoxic conditions and can be used to control vascularization of developing tissues so as to promote vascularization, or directed to damaged tissues or to tissues where de-vasculaization has occurred following damage to the vascular system via an ampuation, stroke, cardiac arrest, extreme hypertension, ischaemia and burns. However, the only hypoxic condition in the experimentation encompasses tumors.

The specification describes the preparation of a retroviral vector, and its transfer to monocyte cell line U937 cells, but does not teach stepwise how this is to be used for therapy. In vitro experiments have also been performed using an adenoviral vector comprising a lacZ gene under the control of a hypoxia regulated promoter-enhancer.

been grown and the effects of hypoxia on macrophage infiltration. Nude mice have an immune system that is non-functional. The immune system of non-nude mice would normally be activated when a virus in introduced, rejecting the virus. Hence the use of nude mice is not an appropriate model for this study. J. Gomez-Navarro et al. in their review article on Gene Therapy for Cancer in 1999, stated that one obstacle that needs to be overcome for curing cancer is the development of better animal models including tumor models in transgenic mice. Hence the results of this study could not be extrapolated to be used for human gene therapy. In addition, details as to therapeutic dosages, length of time the administration of the said vector has to be used to elicit a sustained shrinkage of tumors etc. are lacking. Neither does the specification teach any invivo or exvivo therapy for reduction of tissue tumors by reduction of the infiltration of macrophages to the site of the tumor. Therefore, no working examples have been provided to demonstrate any therapy or the alleviation of any condition associated with hypoxia and/or ischemia and/or stress.

The nature of the invention therefore encompasses methods of administration of a gene *in vivo* or *in vitro* and subsequently observing the results of expression of the gene after transfection. The claims also encompass methods of administering a transfected cell to an individual *in vivo* . The claims additionally encompass vectors that are modified to target a site to which the vector is directed.

In view of the claims directed to transfected macrophges administered, the claims read broadly on the fact that the transfected macrophages are from any

et al. (1995) teaches that when tissues from some species are transplanted into a recipient of a different species, the graft is immediately rejected, whereas with other species combinations a more delayed reaction takes place. They have described the humoral response to xenoantigens and the concept of concordance and discordance among various mammals which serve only as a useful conceptual framework in which to evaluate xenocompatibility. (See page 342 paragraph 1). However because of the unpredictable factors involved with *in vivo* administration of transfected macrophages referred to above, and because the applicants did not support the claimed invention by experimentation, applicants are not enabled for that which is claimed.

The state of the art in gene therapy is still in its infancy and is highly unpredictable. "Clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol" (see Orkin et al. Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, distributed by the National Institutes of Health, Bethesda, MD or www. nih.gov, page 1).

Gene therapy aims to alleviate or cure diseases by altering the genetic makeup of the individual. The first clinical trials for genetic therapy were conducted in 1990. However, there is still no single outcome to point to as a success story after hundreds of clinical trials have been performed worldwide on thousands of individuals. (See Verma, M. et al., Gene Therapy-promises, problems and prospects, Nature Vol. 389 page 239, paragraph # 2). The major problems that have been encountered are (1) the delivery of the altered genes, and (2) the inability to obtain a sustained expression of the

desired protein in a specified location. (See Verma, M. et al., Gene Therapy-promises, problems and prospects, Nature Vol. 389 page 239, paragraph # 5).

Being a new field the amount of direction or guidance necessary in the specification has to be very detailed in order to provide enablement. In this case, the state of the prior art does not teach one skilled in the art how to transfer a gene and induce a therapeutic response. Hence the specification requires detailed methods for preparation of the therapeutic compositions comprising the adenoviral vector, ligand and/or gene, including specific dosages for specific therapies, as claimed by the inventions. This is made clear by the MPEP 608.01(p) where it states: "If the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied...".

The specification does not provide guidance for the selective destroying of mononuclear phagocytes *in-vitro*. Neither does the specification provide guidance for *in-vivo* or *ex-vivo* applications which demonstrate therapy which utilizes the fact that a high macrophage concentration is seen in tumors or any other hypoxic/ischemic or stress site and the treatment is by the administration of a mononuclear phagocyte encoding a specific gene of interest. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 69 recites a method of destroying phagocytes. There are however no

method, for example by cytotoxic genes introduced by means of the mononuclear phagocyte.

Due to the factors discussed above, it would prove an arduous task for one skilled in the art to be able to practice the claimed invention of gene therapy. Since one skilled in the art cannot readily anticipate the results predicted within the subject matter to which the claimed invention pertains, then there is a lack of predictability in the art. Claims 84, 85 are directed to 'pharmaceutical compositions' comprising a (i) regulatable agent and an agent that binds to a cell surface element of a mononuclear phagocyte and reads broadly on a composition which on being administered either ameliorates the symptoms of a disease thus inducing therapy or prevents the onset of a disease. Claims 84, 85 encompass compositions comprising a binding agent such as any viral vector, an adenoviral vector or a lentiviral vector. However the specification does not specifically describe the administration of any viral vector *in vivo* except by prophetic consideration. Due to the unpredictability in the art of administering viral vectors, details of the specific viral vector with specific quantities, specific compositions and sites of delivery are required to be stated precisely in the specification. The results from one viral vector cannot be randomly extrapolated to result in that expected from any viral vector as stated by Verma et al. who stated that the choice of vector will have to be made based on certain criteria such as if the disease is inherited requiring sustained expression or short term expression etc.

In view of the invention directed to methods of *in vivo* and ex vivo gene

transfer, to cell lines in cell culture. The specification teaches in-vitro infiltration of macrophages into tissue biopsies, and taught that a direct correlation exists between macrophage infiltration and tumor angiogenesis. The specification states that this phenomenon of mononuclear phagocytes may be used to deliver drugs to hypoxic/ischaemic sites where mononuclear phagocytes are typically present. However, applicant's disclosure fails to support the claimed invention whereby drugs or prodrugs such as genes encoding a prodrug are delivered in therapeutic compositions resulting in therapy. Due to the unpredictability in the art these *in vitro* examples cannot be extrapolated to that which will take place *in vivo* without undue experimentation.

In view of this, it would prove an arduous task for one skilled in the art to be able to practice the claimed invention of gene therapy. Hence, since one skilled in the art cannot readily anticipate the results predicted within the subject matter to which the claimed invention pertains, then there is a lack of predictability in the art.

In conclusion, given the nature of the invention, the state of the art, the demonstrated lack of predictability of the art, the amount of guidance set forth, the breadth of the claims, and the lack of working examples, one of skill in the art could not make and use the invention without undue experimentation.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 51-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 51-85 either recite the phrase "hypoxia and/or ischemic and/or stress regulatable element" or depend from claims that recite the aforesaid phrase. It is not clear what combination of elements are required and which are not required for the invention to work as claimed. This needs clarification.

Claims 60, 77 recite the term "preferably". This renders the metes and bounds of the claim unclear. It is not clear if the limitation, "the ligand is a mannosylated poly-L-Lysine" following the term "preferably" is part of the claimed invention. See MPEP § 2173.05(d).

Claim 61 recites, "bioreductively activated pro-drug". In the absence of a definition in the specification as to the meaning of this phrase, the metes and bounds of this phrase are unclear.

Claim 65 recites "activating or control product". The specification does not define this phrase, and it is not clear what exactly this phrase encompasses.

8. Claim 68, 69, 70 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: The omitted elements are: What exactly is being provided to the mononuclear phagocyte in step (1)?; OR What is the mononuclear phagocyte being provided to? OR Where is the mononuclear

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 51-53, 56, 60-65, 68, 70, are rejected as the claimed invention is directed to non-statutory subject matter. The claims read on a non-modified mononuclear phagocyte. The claims could be amended to read on a modified phagocyte comprising a heterologous nucleotide of interest, or to recite "isolated" instead.

The claims read on a product of nature because the claims are directed to a mononuclear phagocyte comprising any gene which is regulated by hypoxia. Mononuclear phagocytes naturally migrate to areas of low oxygen supply and with low blood supply. Further limitations recite that the claims encode a p450 enzyme which is one that is found in most cells of normal individuals unless the individual is deficient in a particular p450 enzyme. (See U.S. Pat. NO: 6,309,823). Therefore all limitations recited are components of a non-modified mononuclear phagocyte present in nature.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 51-54, 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferkol. (Proc. Nat. Acad. Sci. Vol. 93, pp. 101-105, Jan 1996, col. 1 and Fig. 1).

Ferkol et al. teach isolated macrophages comprising a gene of interest. Ferkol teach primary macrophages in culture comprising pGL2, and they measured the luciferase gene expression. Ferkol additionally taught BALB/c mice injected with a complex containing pGL2 or pCMV lacZ. Therefore the claims are rejected because they encompass the limitations of the claims and were anticipated by Ferkol.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 51-68, 74-80, 83-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferkol (U.S. 5,972,900) in view of Ratcliffe (U.S. 5,942,434) in view of Leek et al. (Cancer Research 56: 4625-4629, oct. 15, 1996).

Ferkol taught macrophages comprising a DNA complex which had been internalized via receptor mediated gene transfer. Ferkol taught a systemic molecular conjugate consisting

macrophage mannose receptor. Ferkol et al. taught that receptor-mediated gene transfer has been shown to be successful in introducing transgenes into cells *in-vitro*. They taught that this procedure involved linking the DNA to a polycationic protein usually poly-L-lysine containing a covalently attached ligand, which is selected to target a specific receptor on the surface of the tissue of interest. (See col. 1 lines 25-30). Ferkol et al. also taught the tissue specificity of mannosylated DNA complex in targeting DNA to macrophages, which are large scavenger cells or phagocytes. (See col. 5 lines 5-9). They also taught *in vitro* methods for transfecting primary macrophages using the mannose-terminal glycopritein carrier using an expression plasmid pCMVZ. (See col. 28, lines 40-65 and col. 32, lines 17-37). Ferkol also taught nucleic acids encoding an expressible gene which is functional in a target cell, for instance thymidine kinase to ablate specific cells or tissues. (See col. 12 lines 1-10).

Ferkol did not teach the inclusion of a regulatable agent that could be hypoxia, stress or ischemia.

Ratcliffe et al. taught that nucleic acid constructs comprising hypoxia response elements in linkage with a coding sequence of a gene of interest which could encode prodrug activation systems or cytokines, and taught *in-vitro* methods for the same. (See col. 2, lines 30-33). Ratcliffe also taught that several vectors including retroviral vectors could be used as a mechanism for delivery. (See col. 4 line 45). These experiments were conducted in order to measure hypoxically-induced expression of genes. (See Abstract, claims and col, 9 lines 10-15). Ratcliffe also taught inducible/repressible

promoter elements of selectable markers can be used to kill unwanted cells. (See col. 8, lines 65-67).

At the time of the invention, the prevalent thinking was that monocytes enter a tumor and differentiate into macrophages, which preferentially congregate in hypoxic sites deep within the tumor mass far from blood vessels (See reference (2) cited by applicants as stated in specification page 2 lines 17-20: Leek et al. pg. 4626, col. 1, para. 5). Hence, applicants would have been motivated to combine the teachings of Ferkol et al. with that of Ratcliffe, due to its significance to cancer therapy and the current knowledge re macrophage aggregation wherein said macrophage comprises, a hypoxically induced gene to result in the instant invention.

Therefore it would have been *prima facie* obvious at the time the invention was made to combine the teachings of Ferkol, Ratcliffe and Leek resulting in the instant application.

One of ordinary skill in the art would have reasonably expected success in testing the efficacy of the constructs and modified macrophages which would not require undue experimentation.

Therefore, claims 51-68, 74-80, 83-86 are rejected as being obvious.

Conclusion

15. Claims 51-86 are rejected.

16. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

If the claims are amended canceled and/or added the applicants are required to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)* and A CLEAN COPY OF **ALL** PENDING CLAIMS IS REQUESTED to facilitate further examination.

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER